The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

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EMEA PUBLIC STATEMENT ON
LEVACETYLMETHADOL (ORLAAM) - LIFE THREATENING CARDIAC RHYTHM DISORDERS

The European Commission granted a marketing authorisation for the European Union to Sipaco Internacional Lda. on 1 July 1997 for the medicinal product Orlaam, which contains the active substance levacetylmethadol. Orlaam is marketed in Austria, Denmark, Germany, Ireland, The Netherlands, Portugal and Spain.

Orlaam is indicated for the substitution maintenance treatment of opiate addiction in adults previously treated with methadone, as part of a comprehensive treatment plan including medical, social and psychological care. The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP) has been evaluating new safety information as it emerges.

At the time being an estimated 3500 patients in the United States and 700 within the EU are currently treated with Orlaam. Since 1 July 1997, 2 cases of torsade de pointes (a life-threatening cardiac rhythm disorder) and 1 case of sudden death associated with levacetylmethadol administration have been reported.

Following a review of the new safety information, the EMEA wishes to draw attention to the following:

- **Levacetylmethadol should <u>not</u> be administered in patients with known or suspected QT prolongation (corrected QT, QTc> 440 ms), e.g. congenital long QT syndrome, or conditions which may lead to QT prolongation (clinically significant bradycardia less than 50 bpm, any other clinically significant cardiac disease, concomitant treatment with Class I and III anti-arrhythmics).**
- **Levacetylmethadol should <u>not</u> be administered concomitantly with other medicinal products or medical conditions known to prolong the QT interval (see product information indicated below) or known to induce hypokalaemia or hypomagnesaemia.**
- **The patients experiencing symptoms suggesting the occurrence of a severe arrhythmia (torsade de pointes) such as palpitations, dizziness, syncope or convulsion should seek urgent medical advice. Levacetylmethadol should be discontinued, and the patient should be evaluated for QT prolongation and arrhythmias.**

As an urgent measure, the prescribing and patient information has been modified through a rapid procedure at the request of the marketing authorisation holder. The EMEA considers it necessary to provide this new information to the public.

Relevant changes to the product information are indicated below. For the complete scientific evaluation of Orlaam and the complete revised product information see the European Public Assessment Report, also available on the EMEA website.

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PROVISIONAL CHANGES INTRODUCED
TO PRESCRIBING AND PATIENT INFORMATION

INFORMATION TO PATIENTS:

This medication MUST NOT BE USED in the following cases:

- ***patients with known or suspected ECG abnormality (QT prolongation) such as congenital or acquired long QT syndrome or conditions which may lead to QT prolongation:***
- ***a slow heartbeat,***
- ***significant heart disease,***
- ***patients being treated with other medicinal products to control the heart rhythm, or with other medicinal products known to induce ECG abnormality (QT prolongation) (see Interaction with other medicaments and other interactions),***
- ***patients having low blood salts (especially low potassium or low magnesium), being treated with medicinal products known to lower blood salts or having a medical condition that could result in low blood salts (loss of appetite, vomiting and diarrhoea).***

Special warnings:

- ***ORLAAM may make the heart beat irregularly causing you to feel dizzy or have palpitations, feel faint or have convulsions. If it appears you must seek urgent medical advice***.

Interaction with other medicaments and other interactions:

- ***The following medicinal products may induce ECG modifications (QT prolongation) and therefore must never be taken during the course of Orlaam treatment (see section This medication MUST NOT BE USED in the following cases):***

- ***others medicinal products to control the heart rhythm***
- ***medicinal products for the treatment of angina, high blood pressure or an irregular heart beat (calcium channel blockers: bepridil, lidoflazine, prenylamine, terodiline),***
- ***medicinal products for allergies or hay fever (antihistamines: astemizole, terfenadine)***
- ***certain medicinal products for the treatment of mental conditions: certain neuroleptics (chlorpromazine, haloperidol, pimozide, sertindole, sultopride, thioridazine) or certain antidepressants (amitriptyline, doxepin, imipramine, maprotiline),***
- ***antimalarials (chloroquine, halofantrine, quinine)***
- ***other medicinal products (cisapride, erythromycine IV, ketanserin, pentamidine IV, sparfloxacin, spiramycin).***

- ***Medicinal products known to induce low blood salts (especially low potassium or low magnesium) must also never be taken during the course of ORLAAM treatment: diuretics, laxatives or high doses of steroid hormones (fludrocortisone).***

9. DESCRIPTION OF UNDESIRABLE EFFECTS UNDER NORMAL USE

- ***ECG abnormalities, rhythm disturbances of the heart.***

INFORMATION FOR PRESCRIBERS:

4.3 Contra-indications

- ***Patients with known or suspected QT prolongation (corrected QT, QTc> 440 ms), e.g. congenital long QT Syndrome, or conditions which may lead to QT prolongation such as:***
  - ***clinically significant bradycardia (less than 50 bpm),***
  - ***any other clinically significant cardiac disease,***

- ***treatment with Class I and III anti-arrhythmics,***
- ***concomitant treatment with other medicinal products known to prolong the QT interval. These are also listed under section 4.5 (Interaction with other medicinal products and other forms of interaction),***
- ***electrolyte imbalance, in particular hypokalaemia or hypomagnesaemia, and medical conditions or concomitant treatment with medicinal products with the potential of inducing such imbalance. These include anorexia, vomiting and diarrhoea.***

4.4 Special warnings and special precautions for use

WARNINGS:

Cases of QT prolongation and of severe arrhythmia (torsade de pointes) have been observed during treatment with ORLAAM.

ORLAAM should be discontinued if symptoms such as palpitations, dizziness, syncope or convulsion occur, and the patient should be evaluated for QT prolongation and arrhythmias. Reinduction of treatment should be performed as mentioned in section 4.2 (Posology and method of administration).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions between levacetylmethadol and potentially arrhythmogenic medicinal products. Concomitant treatment with the medicinal products mentioned in this section is contraindicated (see section 4.3 – Contra-indications):
- ***class I or III antiarrhythmics***
- ***antihistamines that prolong QT interval (astemizole, terfenadine)***
- ***antimalarials (chloroquine, halofantrine, quinine)***
- ***calcium channel blockers (bepridil, lidoflazine, prenylamine, terodiline)***
- ***neuroleptics that prolong QT interval (chlorpromazine, haloperidol, pimozide, sertindole, sultopride, thioridazine)***
- ***antidepressants (amitriptyline, doxepin, imipramine, maprotiline)***
- ***other medicinal products (cisapride, erythromycin IV, ketanserin, pentamidine IV, sparfloxacin, spiramycin)***

Medicinal products known to induce hypokalaemia or hypomagnesaemia may also precipitate QT prolongation and thus interact with levacetylmethadol - These include:
- ***diuretics and laxatives***
- ***supraphysiological use of steroid hormones with mineralocorticoid potential (e.g. systemic fludrocortisone).***

These lists may not be exhaustive, and any medicinal product known to have the potential to prolong the QT interval should also not be used together with levacetylmethadol.

4.8 Undesirable effects

Incidence less than 1%

Cardiovascular	Postural hypotension, prolongation of the QT ***interval resulting in some cases in severe arrhythmias*** (torsade de pointes), non-specific ST-T wave changes.